

Energy Components of Aqueous Solution: Insight from Hybrid QM/MM Simulations Using a Polarizable Solvent Model

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ABSTRACT: An energy decomposition method is present in statistical Monte Carlo simulations of aqueous solutions of a series of organic solutes, making use of a hybrid quantum mechanical and polarizable molecular mechanical (QM/MM-PIPF) approach. In the hybrid QM/MM-PIPF method, the mutual solute–solvent polarization effect is specifically considered through a coupled iterative procedure that ensures the convergence of solvent induced dipoles and the solute wave function. It should be noted that the method is an approximate approach without specifically considering the electronic correlation effect between solute and solvent electrons, and energetic results have not been verified by free energy calculations. Nevertheless, the energy decomposition analysis provides insight into the details of the molecular polarization effect. Qualitative trends of the energy components from such analyses provide guidance in the understanding of the nature of intermolecular interactions in biomolecular systems, whereas quantitative results on specific terms may be utilized to derive empirical, yet computationally more efficient, force fields. Polarization effects are found to be significant, which contribute 10% to 23% to the total solute–solvent interaction energies. © 1997 by John Wiley & Sons, Inc. *J Comput Chem* **18**: 1061–1071, 1997

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Introduction

Of interest in computer simulation of fluid systems is to examine specific energy components for the interaction between the solute and solvent molecules. This will ultimately lead to a better understanding and reliable prediction of the solvent effect on chemical reactivity.¹ An important contribution to the total energy of the system is the condensed-phase polarization effect; that is, the change of the molecular charge distribution due to solute–solvent interactions.² Several groups have developed methods and parameters of polarizable intermolecular potential functions (PIPF) for organic and biological compounds, whereas a number of recent studies have demonstrated the significance of polarization effects in characterizing intermolecular interactions in solution.^{2–5} A common theme in these studies is that atoms and molecules are treated classically with empirical potential functions. However, the molecular charge polarization is an electronic property and indeed needs to be treated by quantum chemical methods.⁶

In the past 5 years, combined or hybrid quantum mechanical and molecular mechanical (QM/MM) methods have gained increasing attention in molecular simulations.^{6–11} In this approach, the solute molecule is treated quantum mechanically by molecular orbital (MO) theory or other quantum chemical techniques.^{7–9} On the other hand, solvent molecules are approximated by molecular mechanical force fields.¹² Consequently, the change of the solute charge density due to solvation is naturally included in the hybrid QM/MM method. However, the response of the solvent charge distribution has been neglected because of the use of pair potentials in most previous investigations.^{8–10} The popularity of the hybrid QM/MM method is perhaps due to its unique feature of combining both *computational efficiency* of MM force fields and *accuracy* of QM methods for the study of chemical reactions in solution. Furthermore, the procedure can be systematically improved by increasing either the level of the QM treatment of the solute, or the sophistication of the MM force field.¹³

The present article outlines an extension of the hybrid QM/MM potential by including the solvent polarization effect through the use of a polarizable intermolecular potential function for the solvent.^{2–5} Thus, the mutual solute–solvent polar-

ization interaction will be consistently treated in the simulation. This provides us with the opportunity to analyze specific energy components, in particular, the many-body polarization effects in solution. The procedure for implementing a polarizable potential in hybrid QM/MM simulations was originally described in a seminal work by Warshel and Levitt,^{7a} and has been carefully presented in a recent report by Thompson and Schenter.¹¹ The aim of this study is to provide a decomposition analysis of the energetics for a number of organic solutes in aqueous solution to gain insight into the molecular interactions. Although the results and trends of the numerical quantities appear to be reasonable, the validity has not been demonstrated by comparison of solvation free energies with experimental data. The latter calculations are much more demanding the computing resources, and are being pursued in our laboratory. Some elements of the present energy decomposition analysis have been considered in previous studies.^{6,7c} In what follows, the theoretical method and computational procedures are first given, followed by results and discussion.

Methodology

HYBRID QUANTUM AND MOLECULAR MECHANICAL HAMILTONIAN

The use of a hybrid QM/MM potential in fluid simulations has been described by several investigators.^{7–11} Thus, only a brief outline of the method is presented here with emphasis on the use of a polarizable MM potential for the solvent. Following the pioneering work of Warshel and Levitt, and Field et al., a solution system is partitioned into a QM region consisting of the solute molecule, and an MM region containing the rest of the surrounding solvent molecules.⁷ The electronic structure of the solute molecule is described by a Slater determinant wave function Ψ of all occupied molecular orbitals, the latter being a linear combination of an atomic orbital basis set $\{\Phi_\mu\}$. For the MM region, solvent molecules are modeled by empirical force fields.¹² The effective system Hamiltonian is written as follows:

$$\hat{H}_{eff} = \hat{H}_X^o + \hat{H}_{Xs} + \hat{H}_{ss} \quad (1)$$

where \hat{H}_X^o is the Hamiltonian of the solute molecule, \hat{H}_{Xs} is the solute–solvent or QM/MM interaction Hamiltonian describing interactions be-

tween the solute and solvent molecules, and \hat{H}_{ss} is the solvent potential energy. Throughout this article, the subscript X specifies the solute which is treated quantum mechanically, whereas the subscript s represents the classical solvent molecules.

The QM/MM interaction Hamiltonian contains three terms in the present study:

$$\hat{H}_{Xs} = \hat{H}_{Xs}^{v.dW} + \hat{H}_{Xs}^{stat} + \hat{H}_{Xs}^{pol}(\boldsymbol{\mu}) \quad (2)$$

which are, respectively, the van der Waals interaction energy between the solute and solvent atoms, the electrostatic interactions of the solvent point charges with the solute electrons and nuclei, and the interaction between the QM solute and the solvent-induced dipoles $\{\boldsymbol{\mu}_s\}$. Most previous hybrid QM/MM studies utilized pairwise potentials for the MM region without explicit description of the many-body polarization effect. Consequently, only the first two terms in eq. (2) are needed.⁸ In these calculations, the solvent polarization effects are implicitly incorporated into the effective pair potentials through the parameterization step.¹² What is missing is the change of the solvent charge distribution in response to the solvation of a solute molecule.⁸ We note that the van der Waals term in eq. (2) contains empirical parameters, which are introduced to account for the inhomogeneous treatment of QM and MM regions.^{7,8} We have optimized these parameters for the semiempirical AM1 method, as well as those for the *ab initio* 3-21G basis set, in combination with pairwise potentials.¹⁴ With the use of a polarizable solvent model, a new parameter set should be consistently developed for QM atoms. In the present study, we simply used the original values designed for the AM1/TIP3P combination.^{6,14}

The mutual polarization effects between the solute and solvent molecules are specifically determined via the use of a QM/MM polarization Hamiltonian, which is^{7a,8,11}:

$$\hat{H}_{Xs}^{pol}(\boldsymbol{\mu}) = - \sum_{i=1}^N \sum_{s=1}^S \frac{\mathbf{r}_{is} \cdot \boldsymbol{\mu}_s}{r_{is}^3} + \sum_{a=1}^M \sum_{s=1}^S \frac{Z_a \mathbf{R}_{as} \cdot \boldsymbol{\mu}_s}{R_{as}^3} \quad (3)$$

In eq. (3), S , N , and M are the total number of solvent sites, solute electrons, and solute nuclei, respectively; R_{as} and r_{is} are distances of the solute nuclei and electrons from solvent atoms; Z_a are the solute nuclear charges; and $\boldsymbol{\mu}_s$ are atom-centered induced dipoles of the solvent.

The MM energy of a hybrid QM/MM system has been described by Thompson and Schenter in an analogous fashion as in other studies.^{2-5,11} It consists of a pairwise additive term of the familiar Lennard-Jones plus Coulomb form,⁴ and nonadditive polarization terms:

$$\hat{H}_{ss} = \hat{H}_{ss}^{pair} + \hat{H}_{ss}^{pol}(\boldsymbol{\mu}) + \hat{H}_{Xs}^{dist} \quad (4)$$

The pairwise potential is enumerated over pairs of solvent molecules,⁴ whereas the last two terms are polarization energies [eqs. (5) and (6)]^{11,15,16}:

$$\hat{H}_{ss}^{pol}(\boldsymbol{\mu}) = -\frac{1}{2} \sum_{s=1}^S \boldsymbol{\mu}_s \cdot \mathbf{F}_s^o \quad (5)$$

$$\hat{H}_{Xs}^{dist} = \frac{1}{2} \sum_{s=1}^S \boldsymbol{\mu}_s \cdot \mathbf{F}_s^{qm}(\boldsymbol{\Psi}) \quad (6)$$

where \mathbf{F}_s^o and $\mathbf{F}_s^{qm}(\boldsymbol{\Psi})$ are, respectively, the electric fields at the position of atom s due to the permanent solvent charges of all other solvent atoms $\{q_t, t \neq s\}$, and the QM solute wave function $\boldsymbol{\Psi}$. $\boldsymbol{\mu}_s$ are induced dipole moments of solvent atoms. In eq. (6), \hat{H}_{Xs}^{dist} represents the energy costs to polarize the solvent dipoles by the QM (solute) electric field. \hat{H}_{Xs}^{dist} involves interactions between the solute and solvent molecules, although it originates from the enumeration of the solvent polarization energies.^{11,15} This further emphasizes the nonadditive nature of intermolecular interactions in solution.

The induced dipoles are determined self-consistently with an interactive procedure using eq. (7):

$$\boldsymbol{\mu}_s = \alpha_s \left[\mathbf{F}_s^o - \sum_{t \neq s} \mathbf{T}_{st} \cdot \boldsymbol{\mu}_t + \mathbf{F}_s^{qm}(\boldsymbol{\Psi}) \right] \quad (7)$$

where α_s is the atomic polarizability of atom s , and \mathbf{T} is the dipole tensor matrix.¹⁶ The three terms in the brackets yield the total field at position s , which are contributions from the permanent partial charges of the solvent $\{q_s\}$, all other solvent-induced dipoles $\{\boldsymbol{\mu}_t, t \neq s\}$, and the QM wave function and solute nuclear charges. The solvent-induced dipoles depend on the QM solute wave function $\boldsymbol{\Psi}$, whereas the wave function $\boldsymbol{\Psi}$ itself is a function of the solvent-induced dipoles. Thus, eqs. (3) and (7) are coupled, and must be solved iteratively to reach an overall system convergence.

It should be noted that eq. (7) effectively makes use the mean field approximation such that the solvent molecules experience the average electric

field of the QM molecule. Because the time scales for the solvent and solute electronic polarizations are comparable, the procedure neglects the electron correlation effects between the solute and solvent molecules. Furthermore, the short-range exchange repulsion interactions due to the overlap of solute and solvent electron distributions are not explicitly treated in the present hybrid QM/MM approach because the solvent molecules are approximated by classical models. These are important issues which will affect the quantitative results of polarization energies. A proper treatment of these problems would require electron correlation calculations—a computationally daunting and intractable task at the present time in fluid simulations. In hybrid QM/MM potentials, the correlation effect and the exchange repulsion interactions may be approximated in an average way through optimization of the Lennard–Jones parameters to reproduce *ab initio* bimolecular interaction energies as well as solvation free energies. The electric correlation problem has been discussed from different perspectives.¹⁷

ENERGY DECOMPOSITION

Having defined the effective Hamiltonian, we obtain the total energy of the system as the expectation value of the wave function, Ψ [eq. (8)]:

$$\begin{aligned} E_{tot} &= \langle \Psi | \hat{H}_{eff} | \Psi \rangle \\ &= \langle \Psi | \hat{H}_X^o + \hat{H}_{Xs}^{stat} + \hat{H}_{Xs}^{pol} | \Psi \rangle + E_{Xs}^{v dW} \\ &\quad + E_{ss}^{pair} + E_{ss}^{pol}(\boldsymbol{\mu}) + \frac{1}{2} \sum_{s=1}^S \boldsymbol{\mu}_s \cdot \mathbf{F}_s^{qm} \end{aligned} \quad (8)$$

where E_{ss}^{pair} is the pairwise solvent energy from the traditional Lennard–Jones plus Coulombic terms,¹² and $E_{Xs}^{v dW}$ is the van der Waals interaction energy between the QM solute and MM solvent.¹⁴ Both terms, as well as the last two terms in eq. (8), are evaluated classically (although the QM electric fields are determined from the solute wave function).

Although eq. (8) is the working expression for evaluating the total energy of the system during molecular dynamics or Monte Carlo simulations,¹¹ it is difficult to obtain insight into specific energy contributions in the fluid system. Consequently, this has led to decomposing E_{tot} into specific components. After analyzing the energy terms, we found that it is convenient to rewrite eq. (8) in the

following form:

$$E_{tot} = E_X^o(\Psi^o) + E_{Xs} + E_{ss} \quad (9)$$

Here, we have separated the total energy into three components: (1) the intrinsic (gas phase) energy of the solute molecule, $E_X^o(\Psi^o) = \langle \Psi^o | \hat{H}_X^o | \Psi^o \rangle$, where Ψ^o is the wave function of the solute molecule in the gas phase; (2) the solute–solvent interaction energy E_{Xs} ; and (3) the solvent–solvent interaction energy E_{ss} .

Within the decomposition scheme of eq. (9), the solvent energy E_{ss} is defined as follows:

$$E_{ss} = E_{ss}^{pair} + E_{ss}^{pol}(\boldsymbol{\mu}) \quad (10)$$

where $E_{ss}^{pol}(\boldsymbol{\mu})$ is the solvent polarization energy at the solvent configuration of the solution system, excluding the solute molecule (Fig. 1). To examine the mutual solute–solvent polarization effect on the solvent energy, it is of interest to separate $E_{ss}^{pol}(\boldsymbol{\mu})$ into two terms [eq. (11)]:

$$\begin{aligned} E_{ss}^{pol}(\{\boldsymbol{\mu}_s\}) &= E_{ss}^{pol,0}(\{\boldsymbol{\mu}_s^o\}) + \Delta E_{ss}^{pol} \\ &= -\frac{1}{2} \sum_{s=1}^S \boldsymbol{\mu}_s^o \cdot \mathbf{F}_s^o \\ &\quad - \frac{1}{2} \sum_{s=1}^S (\boldsymbol{\mu}_s - \boldsymbol{\mu}_s^o) \cdot \mathbf{F}_s^o \end{aligned} \quad (11)$$

We emphasize that $\{\boldsymbol{\mu}_s^o\}$ are induced dipole moments of the solvent atoms, which are obtained for the solvent configuration in the entire solution system, but, excluding the solute electric field in eq. (7). $\{\boldsymbol{\mu}_s^o\}$ should be clearly distinguished from $\{\boldsymbol{\mu}_s\}$, which are the solvent-induced dipoles of the full QM/MM system. Thus, $\{\boldsymbol{\mu}_s\}$ are converged by including the \mathbf{F}_s^{qm} term in eq. (7). ΔE_{ss}^{pol} gives a measure of the indirect influence of the solute QM electric field on the potential energy of the solvent molecules. It should be mentioned that there is no need to determine $\boldsymbol{\mu}^o$ and $E_{ss}^{pol,0}$ in fluid simulations if the energy decomposition analyses are not performed.

The interaction energy between the QM solute and MM solvent E_{Xs} is particularly interesting in the study of aqueous solvation; however, its definition is not necessarily unique because of the nonadditive nature of the condensed phase polarization effects. Nevertheless, we have compiled all the energy terms containing *explicit* solute and solvent components in the E_{Xs} term. Again, E_{Xs} consists of contributions from the van der Waals ($E_{Xs}^{v dW}$) and electrostatic interactions (E_{Xs}^{el}): $E_{Xs} = E_{Xs}^{v dW} + E_{Xs}^{el}$. Analogous to the analysis outlined in

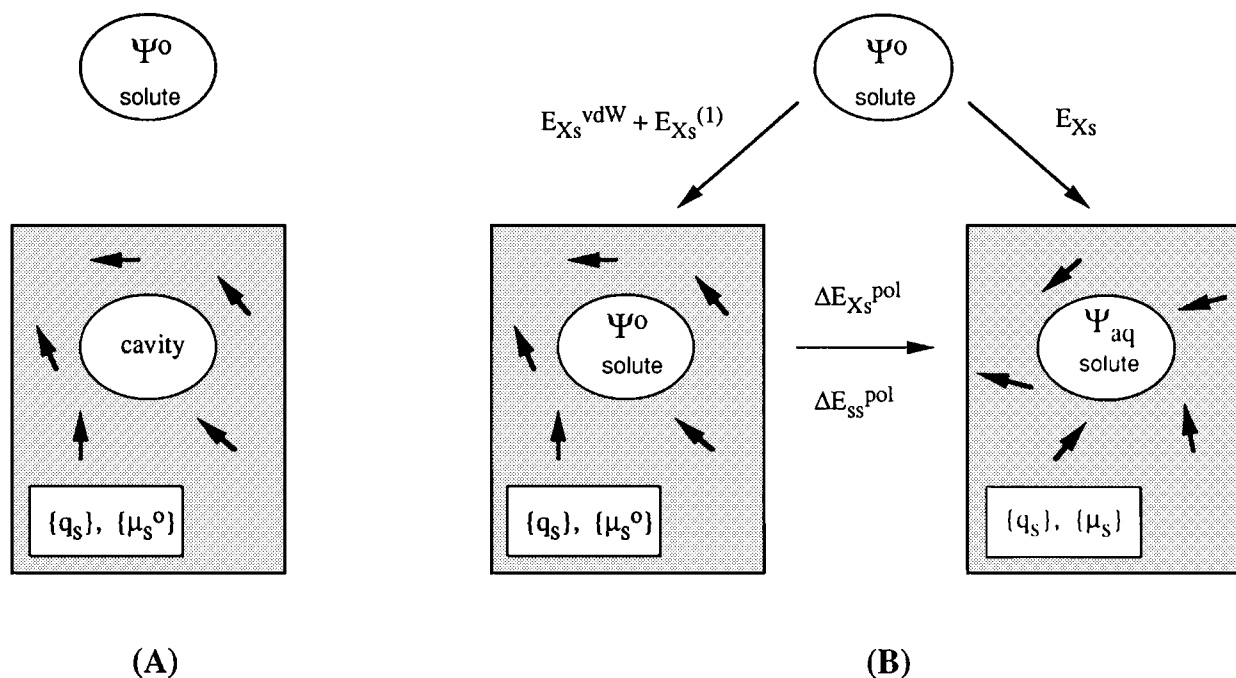


FIGURE 1. Schematic representation of the energy decomposition method. (A) Initial state of the solute in the gas phase, and the solvent system with the solute cavity. (B) The two steps involved in the solvation of a solute in solution. The total solute–solvent interaction energy, E_{Xs} , is determined by: (1) the solvation of the solute in its gas phase charge distribution, followed by (2) the mutual solute–solvent polarization interactions that leads to new charge distributions for the solute along with a change in solvent-induced dipoles.

Gao and Xia,⁶ the electrostatic interaction energy can be represented as follows, which is graphically depicted in Figure 1^{8a}:

$$E_{Xs}^{el} = E_{Xs}^{(1)} + \Delta E_{Xs}^{pol} \quad (12)$$

where $E_{Xs}^{(1)}$ is the first-order perturbation energy, representing interactions between the “unpolarized” QM solute molecule (Ψ^o) and the solvent partial charges $\{q_s\}$ and dipoles $\{\mu_s^o\}$ [eq. (13)].

$$\begin{aligned} E_{Xs}^{(1)} &= E_{Xs}^{stat,0} + E_{Xs}^{pol,0}(\mu^o) \\ &= \langle \Psi^o | \hat{H}_{Xs}^{stat} | \Psi^o \rangle + \langle \Psi^o | \hat{H}_{Xs}^{pol,0}(\mu^o) | \Psi^o \rangle \end{aligned} \quad (13)$$

ΔE_{Xs}^{pol} in eq. (12) is the solute–solvent polarization energy, which involves changes in the solute wave function Ψ^o and the “solvent-only” induced dipoles $\{\mu_s^o\}$ (Fig. 1). The change in molecular charge distributions (Ψ for the QM solute and $\{\mu_s\}$ for the MM solvent) has two energetic consequences [eq. (14)], resulting in: (1) a gain in interaction energy among the molecules involved; and (2) an energy penalty (or distortion energy) to distort the charge distributions. Therefore, the po-

larization energy, ΔE_{Xs}^{pol} , can be decomposed into two terms: (1) a stabilization energy that is gained as a result of the mutual solute–solvent polarization over that of the “unpolarized” solute and “pure” solvent [eq. (15)]; and (2) an electron distortion energy, ΔE_{dist} [eq. (16)]. The distortion energy includes energies invested in changing the solute wave function from the gas phase equilibrium state, Ψ^o , to that in solution Ψ , and the solvent dipoles from $\{\mu_s^o\}$ to $\{\mu_s\}$. It is important to point out that the total polarization energy, ΔE_{Xs}^{pol} , is always less than or equal to zero, providing a net stabilization to the system.

$$\Delta E_{Xs}^{pol} = \Delta E_{stab} + \Delta E_{dist} \quad (14)$$

$$\Delta E_{stab} = \Delta E_{stab}^{stat} + \Delta E_{stab}^{pol} \quad (15)$$

$$\Delta E_{dist} = \Delta E_X^{dist} + \Delta E_{Xs}^{dist} \quad (16)$$

Here, in eq. (15), $\Delta E_{stab}^{stat} = \langle \Psi | \hat{H}_{Xs}^{stat} | \Psi \rangle - \langle \Psi^o | \hat{H}_{Xs}^{stat} | \Psi^o \rangle$, and $\Delta E_{stab}^{pol} = \langle \Psi | \hat{H}_{Xs}^{pol}(\mu) | \Psi \rangle - \langle \Psi^o | \hat{H}_{Xs}^{pol}(\mu^o) | \Psi^o \rangle$. These two components are contributions from the solvent partial charges $\{q_s\}$ and induced dipoles $\{\mu_s\}$, respectively. The ΔE_X^{dist} term in eq. (16) is the energy cost for distorting the

solute electron distribution in solution, which is given as follows:

$$\Delta E_X^{dist} = \langle \Psi | \hat{H}_X^o | \Psi \rangle - \langle \Psi^o | \hat{H}_X^o | \Psi^o \rangle \quad (17)$$

As noted before [eq. (6)], the second term in eq. (16) represents the energy cost for the QM system to polarize the MM solvent dipoles.¹⁵ It has been emphasized by Thompson and Schenter that, at convergence of both the QM and MM system, the following equality exists¹¹:

$$\Delta E_{Xs}^{dist} = -\frac{1}{2} \langle \Psi | \hat{H}_{Xs}^{pol}(\boldsymbol{\mu}) | \Psi \rangle \quad (18)$$

Note that the classical and quantum energies are evaluated independently in our hybrid QM/MM computations. Eq. (18), nevertheless, provides a useful test of the overall system convergence of the mutual QM/MM polarization.

Computational Details

Implementation of the MM polarization term in QM calculations [eq. (3)] involves the introduction of one-electron integrals of the form $I_{\sigma\lambda} = \langle \Phi_\sigma | \mathbf{r} \cdot \boldsymbol{\mu} / r^3 | \Phi_\lambda \rangle$ into the Fock matrix.^{8,11} It turns out that the QM electric field at an MM site, which is defined as the negative of the gradient of the QM electrostatic potential, requires the same integrals. In practice, we have taken an approximation used earlier by Thompson and Schenter, in which the solvent point dipole at an MM site is expanded as a set of six point charges aligned along the Cartesian axes and each 0.1 Å from the dipole center.¹¹ The approximation can be made sufficiently accurate by adjusting the separation of the expansion point charges. Consequently, the simple point charge integrals in molecular orbital calculations can be used directly. Within the semiempirical NDDO approximation employed in the MNDO or AM1 method,^{18,19} Thompson also noted that the point charge expansion of the integral $I_{\sigma\lambda}$ is equivalent to the two-electron integral ($\sigma\lambda$, sp) as determined by the method of Dewar and Thiel.^{20,21} Thus, analytical expressions can be used, which is necessary in molecular dynamics simulations.

Bakowies and Thiel recently presented an optimization of the semiempirical treatment of electrostatic potentials and fields for combined QM/MM calculations.²² Their procedure is based on that proposed by Ford and Wang,²³ and aimed at reproducing *ab initio* HF/6-31G(d) electrostatic po-

tentials for a variety of organic compounds with the AM1 or MNDO method. In our computation, the interaction energy between the QM solute and MM solvent is directly determined in QM calculations.²⁴ Consequently, the following equality holds along with that of eq. (18) at convergence of the QM and MM systems¹¹:

$$\sum_{s=1}^S q_s \Phi_s = \langle \Psi | \hat{H}_{Xs}^{el} | \Psi \rangle \quad (19)$$

where Φ_s is the electrostatic potential at position s . Eqs. (18) and (19) are consequences of classical (the left-hand side of the equations) and quantum (the right-hand side) representations of the same quantities. Therefore, in our approach, these two equations ensure that the electric field obtained from the semiempirical wave function, Ψ , can be directly used in MM polarization calculations.

The key in hybrid QM/MM-PIPF calculation is to achieve the energy convergence of the entire hybrid QM/MM system. Therefore, a double-iterative procedure is used,¹¹ and is outlined as follows:

1. For each Monte Carlo step, the MM polarization energy [eqs. (5) and (6)] is first brought to convergence through an iterative process by introducing the QM solute electric field, $\mathbf{F}^{qm}(\Psi^m)$, in eq. (7),^{2,5} where Ψ^m is the solute wave function from the previous Monte Carlo configuration, or that generated in iteration m of the QM/MM system (step 3). The convergence of $\{\boldsymbol{\mu}_s\}$ in the MM system is determined by a root-mean-square (rms) difference of less than 5×10^{-4} D/molecule in induced dipole between successive iterations. In this step, the QM wave function is held fixed, or $\mathbf{F}^{qm}(\Psi^m)$ is treated as an "external" field to the MM solvent system. Three or four iterations are sufficient to get $\{\boldsymbol{\mu}_s^m\}$ to converge in the first cycle, and only one or two iterations are enough subsequently.
2. The resulting solvent-induced dipoles $\{\boldsymbol{\mu}_s^m\}$ from step 1 along with the permanent point charges $\{q_s\}$ are employed to evaluate the one-electron integrals, and are then included in the QM Hartree-Fock (HF) SCF calculation. This leads to a new wave function, Ψ^{m+1} , for the QM system, which can be used in the next MM iteration in step 1.

Standard criteria on the convergence of the QM density matrix as implemented in the MOPAC program are applied in this study.²⁵

3. The full QM/MM system convergence is determined by a change of less than 0.01 kcal/mol in the QM energy between two QM HF-SCF iterations. Then, the converged energy of the system is used in the Monte Carlo process. If the system convergence in this step is not achieved, steps 1 and 2 are repeated. We found that the total energy of the system converges extremely fast, requiring one or two cycles. For simulations of aqueous solution, the use of a polarizable water model takes about five to ten times more computational time than nonpolarizable models in a hybrid AM1/MM approach.

The hybrid QM/MM-PIPF potential has been implemented into the MCQUB program in our laboratory,^{26a} in which the quantum mechanical energies are determined with the semiempirical AM1 method using the MOPAC program developed by Stewart.^{19,25} The Metropolis Monte Carlo criteria were tested with the BOSS program.^{26b} In the present study, the polarizable water model, POL2, developed by Dang is adopted to represent the solvent molecules.^{27a} The POL2 model makes use of the simple-point-charge (SPC) water geometry,²⁸ with permanent partial charges and isotropic atomic polarizabilities located on each atom. The model was shown to yield reasonable results for simulations of liquid water, and has been used in several applications.²⁷ Statistical Monte Carlo simulations are carried out for a cubic box containing 210 POL2 water molecules plus one QM-AM1 solute. Periodic boundary conditions are used along with the NPT ensemble at 1 atm and 25°C.²⁹ A spherical cutoff distance of 8.5 Å is employed for both solute-solvent and solvent-solvent interac-

tions. To facilitate the statistics near the solute, the Owicki-Scheraga preferential sampling technique is used such that solvent moves are made proportional to $1/(r^2 + C)$, where $C = 150 \text{ Å}^3$.³⁰ Each simulation was first equilibrated for 5×10^5 configurations using the hybrid AM1/TIP3P (non-polarizable solvent) potential,³¹ followed by at least 5×10^5 configurations using the hybrid AM1/POL2 potential. Ensemble averages are then collected in the next 1.5×10^6 configurations of Monte Carlo simulations. Statistical errors are determined from fluctuations of averages of 10^5 configuration blocks. All computations are carried out on IBM RS6000/370 workstations in our laboratory.

Results and Discussion

Table I lists the energy components of the total average energies obtained from Monte Carlo simulations of a series of six organic compounds in aqueous solution. Table I provides a good indication of the relative contributions of the pairwise potential and polarization effects to the total energy of the system. We note that, in the past, the total energy of a solution has been used to compute the enthalpy of solvation, by subtracting the energy of the pure solvent. However, this strategy has been abandoned because of the huge computational uncertainties, and is replaced by the free energy perturbation method.³² In the hybrid QM/MM simulation, the polarization energy typically makes up about 30% of the total potential energy of each solution using Dang's POL2 potential.²⁷

Components of the solute-solvent interaction energy are given in Table II, which includes the van der Waals term and the electrostatic term. The latter is further divided into the polarization energy ΔE_{Xs}^{pol} , and the "permanent" electrostatic in-

TABLE I.
Energy Components of Aqueous Solution (kcal/mol).

Solute	E_{tot}	$E_X^o(\Delta H_f^o)$	E_{ss}^{pair}	E_{ss}^{pol}	E_{Xs}
H ₂ O	-2273.8 ± 2.9	-59.2	-1515.7 ± 2.9	-684.6 ± 2.4	-14.3 ± 0.4
CH ₃ OH	-2265.0 ± 2.6	-57.0	-1509.9 ± 2.6	-683.5 ± 1.5	-14.6 ± 0.3
CH ₃ CH ₃	-2209.5 ± 1.9	-17.4	-1509.7 ± 1.9	-679.4 ± 1.4	-3.0 ± 0.1
CH ₃ COCH ₃	-2228.7 ± 4.1	-48.5	-1493.8 ± 4.1	-672.2 ± 2.7	-14.2 ± 0.3
CH ₃ CONHCH ₃	-2232.1 ± 3.3	-47.3	-1496.7 ± 3.3	-664.9 ± 1.6	-23.3 ± 0.6
NH ₂ CH=CHCHO	-2216.2 ± 3.9	-24.7	-1490.4 ± 3.9	-665.2 ± 2.3	-35.9 ± 1.1

teraction energy, $E_{Xs}^{(1)}$, resulting from the solvent permanent charges and the “initial” solvent induced dipoles $\{\mu_s^o\}$, [eq. (12)]. In all cases examined in this study, the van der Waals term makes substantial contributions to the total solute–solvent interaction, except for water, which has a slight destabilization effect. Of particular interest is the electrostatic contribution, for which the predominant component is due to the $E_{Xs}^{(1)}$ term. The first order perturbation energy $E_{Xs}^{(1)}$ has a much greater contribution from the solvent partial charges $\{q_s\}$ [eq. (13)] than the interaction energy due to the solvent-induced dipoles $\{\mu_s^o\}$. This may be understood in that the solvent-induced dipoles $\{\mu_s^o\}$, which are determined for the solvent in the configuration of the solution, are not necessarily aligned in favorable orientations for solute–solvent interactions. The energies defined in eq. (13) correspond to the process of transferring the solute molecule from the gas phase into aqueous solution, whereas the charge distributions of the solute and solvent are kept fixed in their separate states (Fig. 1).

These charge distributions will be altered owing to solute–solvent interactions. The energy change accompanying the charge reorganization, in terms of the wave function Ψ for the solute and induced dipoles $\{\mu_s\}$ for the solvent, can be attributed to the mutual solute–solvent polarization effect (Fig. 1). From Table II, it is clear that the polarization components are not negligible, and constitute 10% to 23% of the total solute–solvent interaction energies, except for the hydrophobic solute, ethane. As expected, the largest polarization effect occurs in conjugated systems including *N*-methylacetamide (NMA) and 3-aminopropenal, in which the polarization energy contributes 18% and 23% to the total solute–solvent interaction energy, or 24% and 27% of the electrostatic interaction energies, respectively.

Tables III and IV yield additional insights into the molecular polarization between the solute and solvent systems. The polarization energy, ΔE_{Xs}^{pol} , contains a stabilization component and an energy penalty [eq. (14)]. The overall effect is demonstrated in Table III for the computed solute–solvent polarization energies, ΔE_{Xs}^{pol} , which are negative or favorable for all systems from our numerical simulations. Both the solvent point charges and induced dipoles make significant contributions to the polarization of the solute wave function, as revealed by the comparable sizes of the ΔE_{stab}^{stat} and ΔE_{stab}^{pol} terms [eq. (15)]. This contrasts the relative contributions to the $E_{Xs}^{(1)}$ term from the two components, $\{q_s\}$ and $\{\mu_s^o\}$; the latter is only about 15% of the former (Table II). Along with the observation of small changes in the solvent–solvent polarization energy, ΔE_{ss}^{pol} , upon dissolution of the solute (Table IV), these results suggest that the orientations of the solvent dipoles display much greater effects on the solute polarization than the magnitude of these dipoles.

It is of interest to make an additional observation regarding the ΔE_{ss}^{pol} term (Table IV), which represents the indirect influence of the solute molecule on the medium—the solvent. Although ΔE_{ss}^{pol} comes from the solvent–solvent interactions, it is a result of the solute–solvent mutual polarization. This, again, further emphasizes the nonadditive nature of molecular interactions in solution. However, in pairwise MM force fields, this effect is completely ignored, leaving doubt in regard to computational results for systems involving significant changes in the molecular environment. Interestingly, inclusion of the solute electric field enhances the solvent polarization and increases the solvent polarization energy for the systems considered in this study.

A further measure of the molecular polarization is provided by the computed changes in molecular

TABLE II.
Energy Components of Solute–Solvent Interactions (kcal / mol).

Solute	E_{Xs}	E_{Xs}^{dW}	E_{Xs}^{el}	$E_{Xs}^{(1)}$	$E_{Xs}^{stat,0}$	$E_{Xs}^{pol,0}$	E_{Xs}^{pol}
H ₂ O	−14.3 ± 0.4	0.1 ± 0.1	−14.4 ± 0.4	−12.7 ± 0.3	−11.0 ± 0.3	−1.7 ± 0.1	−1.7 ± 0.3
CH ₃ OH	−14.6 ± 0.3	−2.4 ± 0.1	−12.1 ± 0.3	−10.3 ± 0.2	−8.6 ± 0.2	−1.7 ± 0.1	−1.8 ± 0.2
CH ₃ CH ₃	−3.0 ± 0.1	−4.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	0.0 ± 0.0	−0.1 ± 0.0
CH ₃ COCH ₃	−14.2 ± 0.3	−6.1 ± 0.1	−8.1 ± 0.3	−6.6 ± 0.4	−5.9 ± 0.3	−0.7 ± 0.1	−1.5 ± 0.2
CH ₃ CONHCH ₃	−23.3 ± 0.6	−5.8 ± 0.1	17.4 ± 0.5	−13.3 ± 0.3	−11.8 ± 0.3	−1.5 ± 0.1	−4.1 ± 0.5
NH ₃ CH=CHCHO	−35.9 ± 1.1	−5.8 ± 0.1	−30.0 ± 1.0	−21.8 ± 0.5	−19.5 ± 0.5	−2.3 ± 0.1	−8.2 ± 0.9

TABLE III.
Energy Components of Solute–Solvent Polarization Energies (kcal / mol).

Solute	E_{Xs}^{pol}	ΔE_{stab}	ΔE_{stab}^{stat}	ΔE_{stab}^{pol}	ΔE_{dist}	ΔE_X^{dist}	ΔE_{Xs}^{dist}
H ₂ O	-1.7 ± 0.3	-5.7 ± 0.2	-2.8 ± 0.1	-2.9 ± 0.2	4.0 ± 0.1	1.7 ± 0.1	2.3 ± 0.1
CH ₃ OH	-1.8 ± 0.2	-6.2 ± 0.2	-3.2 ± 0.1	-3.0 ± 0.2	4.4 ± 0.1	2.0 ± 0.1	2.4 ± 0.1
CH ₃ CH ₃ ^a	-0.13	-0.30	-0.27	-0.03	0.17	0.15	0.02
CH ₃ COCH ₃	-1.4 ± 0.2	-4.2 ± 0.2	-2.3 ± 0.1	-1.9 ± 0.1	2.7 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
CH ₃ CONHCH ₃	-4.1 ± 0.5	-11.5 ± 0.4	-6.5 ± 0.3	-4.9 ± 0.3	7.4 ± 0.3	4.1 ± 0.2	3.2 ± 0.1
NH ₂ CH=CHCHO	-8.2 ± 0.9	-22.6 ± 0.8	-13.8 ± 0.7	-8.8 ± 0.4	14.4 ± 0.4	8.9 ± 0.3	5.5 ± 0.2

^a Standard errors are 0.01 to 0.02 kcal / mol for these energies.

dipole moment (Table V), or induced dipoles due to solvation, $\mu_{ing} = \mu_{aq} - \mu_{gas}$. For the symmetric ethane molecule, the average of instantaneous dipole vectors yields an aqueous dipole moment close to zero. In other cases, the aqueous dipole moments are 30% to 70% greater than those in the gas phase, which are consistent with early observations.⁶ As expected, the largest effects are for molecules containing π delocalizations. For 3-amino propenal, the dipole moment in water is 9.5 D, which is 3.9 D larger than the gas phase value.

Using a fluctuating charge (FQ) model, Rick and Berne examined the polarization effect on amides in aqueous solvation.⁵ The computed induced dipole moment for *trans*-NMA is 2.2 D in that study. Considering the large increase μ , the agreement with our estimate of 1.71 ± 0.04 D, which employs the QM AM1 wave function for the solute and an entirely different polarizable potential for water, seems to be reasonable. Interestingly, our early study using the pairwise TIP3P water model also yielded a μ_{ind} of 1.7 D for NMA.⁶ Rich and Berne also reported a polarization free energy of +1.4 kcal/mol for NMA, which is defined as the free energy to change the charges of the solute from the gas phase to aqueous phase

values.⁵ Because our study is restricted to the energies of the system, a direct comparison with our results is not appropriate. However, it should be pointed out that the definition of polarization energy by these investigators [eq. (2.4) of Rick and Berne^{5a}] is equivalent to the ΔE_X^{dist} term in the present work [eq. (17)]. Inspecting Table III, it turns out that the total polarization energies for solute–solvent interactions, ΔE_{Xs}^{pol} , are numerically similar to ΔE_X^{dist} , although differ by a sign.

The energy decomposition of eq. (9) is particularly useful in that it separates the intrinsic (gas phase) energy of the solute molecule from energies related to the solvation process. Consequently, it allows the energy and geometry determined at a different theoretical level to be used to represent the intrinsic properties of the solute, whereas the solute–solvent interaction energy can be determined with the semiempirical QM methods in fluid simulations. In cases where semiempirical methods yield poor results for the solute molecule, high level *ab initio* calculations can be used to determine $E_X^o(\Psi^o)$. This has been discussed previously, and is generally recommended in studying complex organic reactions.^{8a} Thus, the semiempirical QM method implemented in hybrid QM/MM

TABLE IV.
Energy Components of Solvent Polarization Energies (kcal / mol).

Solute	E_{ss}^{pol}	$E_{ss}^{pol,0}$	ΔE_{ss}^{pol}	$\langle \Psi \hat{\mu}_{Xs}^{pol} \Psi \rangle$	ΔE_{Xs}^{dist}
H ₂ O	-684.6 ± 2.4	-683.6 ± 2.4	-1.0 ± 0.1	-4.7 ± 0.2	2.3 ± 0.1
CH ₃ OH	-683.5 ± 1.5	-682.4 ± 1.5	-1.1 ± 0.1	-4.7 ± 0.1	2.4 ± 0.1
CH ₃ CH	-679.4 ± 1.4	-679.4 ± 1.4	-0.02 ± 0.01	-0.04 ± 0.01	0.02 ± 0.01
CH ₃ COCH ₃	-672.3 ± 2.7	-671.8 ± 2.7	-0.5 ± 0.1	-2.6 ± 0.1	1.3 ± 0.1
CH ₃ CONHCH ₃	-664.9 ± 1.6	-663.8 ± 1.6	-1.1 ± 0.1	-6.5 ± 0.3	3.1 ± 0.1
NH ₃ CH=CHCHO	-665.2 ± 2.3	-663.5 ± 2.3	-1.7 ± 0.1	-11.1 ± 0.4	5.5 ± 0.2

TABLE V.
Computed Molecular Dipole Moments (Debye Units).

Solute	$\mu(\text{gas})$	$\mu(\text{exp})$	$\mu(\text{aq})$	$\Delta\mu_{\text{ind}}$
H ₂ O	1.85	1.85	2.16 ± 0.01	0.31 ± 0.01
CH ₃ OH	1.62	1.70	2.11 ± 0.01	0.49 ± 0.01
CH ₃ CH ₃	0.0	0.0	0.05 ± 0.01	0.05 ± 0.01
CH ₃ COCH ₃	2.75	2.88	3.61 ± 0.03	0.86 ± 0.03
CH ₃ CONHCH ₃	3.51	3.85	5.22 ± 0.04	1.71 ± 0.04
NH ₃ CH=CHCHO	5.56		9.26 ± 0.10	3.70 ± 0.10

simulations may be considered a sophisticated procedure to evaluate solute–solvent interaction energies.

Because the QM/MM interaction Hamiltonian contains empirical parameters in the form of the Lennard–Jones terms [eq. (2)], QM/MM (solute–solvent) interaction energies can be optimized to reach a level of accuracy that is comparable to the energetics of the solvent–solvent potentials.¹⁴ Therefore, it is critical to simultaneously improve the accuracy of the MM force field,¹² and to increase the complexity of the QM algorithm (*ab initio* and density functional) in a hybrid QM/MM potential. It is the balance of solute–solvent and solvent–solvent interactions that determines the outcome of fluid simulations. In practice, due to the limitation of computational speed, semiempirical QM algorithms are perhaps the only practical choice at the present time for simulations of large molecules of biological interest.

Conclusions

In this study, we have carried out simulations of dilute aqueous solutions of organic compounds, making use of a combined QM Hartree–Fock and MM potential with a polarizable intermolecular potential for the solvent. In such a hybrid QM/MM approach, the mutual solute–solvent polarization effects are specifically considered in the forms of the change in molecular wave function for the solute, and induced poles for the solvent. For each configuration in our Monte Carlo simulation, the energy of the entire QM and MM-PIPF system is fully converged through a coupled iterative procedure that has been used by Thompson and Schenter.¹¹ Undoubtedly, the method employed in this study represents a logical step forward toward systematic improvement of the representation and accuracy of the potential energy surface for chemical systems in condensed phases. Although the

increased complexity of the hybrid QM/MM approach requires additional computational resources, the insight gained from these calculations, as demonstrated by the energy decomposition analysis presented here, is clearly valuable. The qualitative trends of the energy components provide guidance in the understanding of the nature of intermolecular interactions in biomolecular systems, whereas the quantitative results found for specific terms may be utilized to derive empirical, yet computationally more efficient, force fields.

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